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Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction†

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Aims To compare quality of life (QoL) in heart failure (HF) patients with preserved ejection fraction (HF-PEF) and HF patients with reduced ejection fraction (HF-REF) in a well-defined HF population.

Methods and results Patients with HF-PEF [left ventricular ejection fraction (LVEF) $\geq$40%] were matched by age and gender to patients with HF-REF (LVEF $<$40%). In the current study, we only included HF patients with a B-type natriuretic peptide level (BNP) $>$100 pg/mL. Quality of life was assessed by Cantril's Ladder of Life, RAND-36, and the Minnesota Living with Heart Failure questionnaire, and impairment of QoL was adjusted for by BNP as a marker for severity of HF. We examined a total of 290 HF patients, of whom 145 had HF-PEF (41% female; age 72 $\pm$ 10; LVEF 51 $\pm$ 8%) and 145 had HF-REF (41% female; age 73 $\pm$ 10, LVEF 26 $\pm$ 7%). All HF patients reported markedly low scores of QoL, both on the general and disease-specific QoL questionnaires. Quality of life between patients with HF-PEF and HF-REF did not differ significantly. When adjusting the QoL scores for BNP, an association between QoL and LVEF was not found, i.e. patients with HF-PEF and HF-REF with similar BNP levels had the same impairment in QoL.

Conclusion Quality of life is similarly impaired in patients with HF-PEF as in HF-REF. These findings further support the need for more pharmacological and non-pharmacological studies in patients with HF-PEF.
Trial registration number: NCT 98675639.

Keywords Heart failure • Quality of life • Preserved ejection fraction • Reduced ejection fraction • B-type Natriuretic Peptide

Introduction

Heart failure (HF) has a major impact on the quality of life (QoL) of patients, in physical, mental, and social domains.[1,2] Patients with HF have a significantly lower QoL than an age- and gender-matched members of the community.[3] But even compared with other chronically ill patients, patients with HF have similar or even more impaired physical and mental health.[4] In recent years, patient-centred outcomes, such as QoL, have gained greater importance, particularly because life expectancies for HF patients have increased, and HF patients have to adjust to living with a chronic condition and for many (elderly) patients QoL appears to be more important than longer survival.[5,6] In addition, impaired QoL is increasingly associated with a poor outcome in HF.[7,8]

In HF patients, the large majority of studies have been conducted in patients with a reduced ejection fraction (HF-REF). However, at least 50% of all HF patients have HF with a preserved ejection fraction (HF-PEF).[9,10] Symptoms and signs often seem similar in patients with HF-PEF and HF-REF.[11] However, no treatment has been shown to be effective in HF-PEF patients, and current guidelines do not support the use of any class of drugs in this patient category.[1] There is only limited knowledge about the QoL of patients with

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HF-PEF compared with patients with HF-REF. Five studies that compared QoL in these two populations showed inconsistent results, reporting either no significant differences in QoL[11–14] or more impaired QoL in patients with HF-REF.[15].

Previous reports about the QoL of patients with HF-PEF were not only relatively small, but they also used the New York Heart Association (NYHA) functional class to adjust for severity of HF, which of course affects QoL as well. Indeed, none of the aforementioned studies used an objective diagnostic marker for the severity (and presence) of HF. Especially in patients with HF-PEF, the diagnosis of HF is often more difficult, and in fact some patients with assumed HF-PEF do not have HF but suffer from other conditions such as anaemia, lung disease, or even depression.[9,10].

We therefore studied a large number of QoL measurements in a group of patients with HF-PEF, compared with a matched group of patients with HF-REF. In order to try to obtain an objective parameter for the severity of HF, we used plasma levels of B-type natriuretic peptide (BNP), since this is an independent and reliable marker of HF severity.[16].

Methods

Patient population

Data from patients participating in the COACH (Coordinating study evaluating Advising and Counselling in Heart failure) study were used. COACH was a multicentre, randomized clinical trial on the effect of a disease management programme in HF, the design and main results have been published.[17,18] In short, 1023 patients from 17 hospitals in the Netherlands were enrolled in the COACH study. Patients were included in the study at the end of hospitalization for HF (NYHA functional Class II–IV), with HF as the primary diagnosis. The diagnosis was based on a combination of typical signs and symptoms according to the European Society of Cardiology guidelines[1] for which a hospital stay was considered necessary, and the need for intravenously administered medication. During hospitalization, all patients received standard care, both pharmacological, and non-pharmacological, according to the guidelines[1] in a cardiology ward, staffed by cardiologists and registered nurses. Patients were 18 years or older and had evidence of structural underlying heart disease as shown at cardiovascular imaging. Exclusion criteria were: concurrent inclusion in a study requiring additional visits to research health care personnel; restrictions that made the patient unable to fill in data collection forms; invasive intervention within the last 6 months or planned during the following 3 months; or ongoing evaluation for heart transplantation. All patients gave written informed consent. Although all patients in the COACH study had HF as the primary diagnosis and were included in experienced HF centres, in the current analyses we only included patients who had a BNP plasma level >100 pg/mL, to strengthen the evidence for a diagnosis of HF in all patients.[1,19].

The study was performed in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Medical Ethics Committee in each participating centre.

Data collection

Left ventricular ejection fraction and brain natriuretic peptide

Data on left ventricular function (LV function) were obtained by standard trans-thoracic echocardiography. These data were used to distinguish between HF-PEF and HF-REF. Reduced LV systolic function was defined as a LV ejection fraction (LVEF) $<40\%$ (HF-REF); and preserved LV systolic function was defined as an LVEF $\geq 40\%$ (HF-PEF). In the current analyses, only patients with complete echocardiographic data were included. Plasma BNP levels were determined within 4 h of blood collection (1 mL blood, collected in EDTA), on the day of hospital discharge or on the day before hospital discharge. All BNP measurements were performed using a fluorescence immunoassay kit (Triage®; Biosite Incorporated, San Diego, CA, USA).[19].

Quality of life

Data on QoL in the COACH study were collected during the index hospitalization and during follow-up. To minimize the confounding effect of the recent hospitalization on QoL, we used QoL data collected 1 month after discharge. Quality of life was assessed in three different ways: global well-being, general QoL, and disease-specific QoL.

Global well-being was assessed by Cantril's Ladder of Life. This is a single-item measure which asks the patient to rate their sense of well-being on a ladder, with 10 reflecting the best possible life imaginable and 0 reflecting the worst possible life imaginable. A higher score indicates better well-being.[20].

General QoL was assessed by the Medical Outcome Study 36-item General Health Survey (RAND-36), a self-report questionnaire of general health status. It is a well-validated generic, 36-item questionnaire that includes nine health concepts that represent dimensions of QoL: physical functioning, social functioning, role limitations because of physical functioning, role limitations because of emotional functioning, mental health, vitality, bodily pain, general health, and perceived health change. Each dimension has a score between 0 and 100; a higher score means better health.[21].

Disease-specific QoL was measured by means of the Minnesota Living with Heart Failure (MLwHF) questionnaire.[22] The MLwHF questionnaire is a 21-item questionnaire assessing how HF has affected the life of the respondent during the last month. The MLwHF has a scoring range of 0 for no impairment as a result of HF to 105 for maximum impairment. The questions cover symptoms and signs relevant to HF, physical activity, social interaction, sexual activity, work, and emotions. Three scores can be determined: an overall score (21 items, 0–105), the physical dimension (8 items, 0–40), and the emotional dimension (5 items, 0–25). Higher MLwHF scores mean a worse QoL.

Statistical analysis

The two patient groups (HF-PEF and HF-REF) were matched by age (10 year categories) and gender to have a fair test of differences.[23] First, descriptive statistics were used to characterize the HF-PEF and HF-REF patients. For continuous variables means and standard deviations and for categorical variables frequencies with percentages were used. Secondly, differences in QoL between both HF patient groups were tested univariately using the Mann–Whitney *U* test. Thirdly, a Spearman correlation was calculated between BNP and QoL in the total group to analyse the relation between QoL and BNP levels. Finally, to adjust for an objective measure of the severity of HF, an analysis of covariance was performed using QoL scores as the dependent variable and BNP as the covariate. The more subjective measure for the severity of HF, NYHA functional class, was not included in the analysis because of an overlap with (physical dimensions of) QoL.

Analyses were performed using SPSS for windows version 16 (SPSS Inc., Chicago, IL, USA). Outcomes were considered statistically significant when $P < 0.05$.

Results

Patients

Of the 1023 patients included in the main COACH study, an LVEF measurement and a BNP level were available in 698 patients. Of these, 627 patients had a BNP level >100 pg/mL. Within this patient sample, QoL questionnaires at 1 month after discharge were completed by 485 patients. Only patients who completed all questionnaires were included in the current study. Of these, 31% had an LVEF ≥40 and 69% had an LVEF <40%.

After matching for age and gender, both patient groups consisted of 145 patients. Due to the process of matching, 195 HF patients (190 LVEF <40%, 5 LVEF ≥40%) were not analysed. These excluded HF patients who were younger, more often male, had a lower mean LVEF, and their QoL was slightly better on physical functioning of the MLwHF questionnaire. ($P < 0.05$). All other domains of QoL, and the BNP levels were similar in both groups.

Characteristics

Patients with HF-PEF were on average 72 (±10) years old, 41% were female, and the mean LVEF was 50% (±8%). Patients with HF-REF were on average 72 (±10) years old, 41% were female, and the mean LVEF was 26% (±7%) (*Table 1*). In patients with HF-PEF the prevalence of hypertension was higher than in patients with HF-REF ($P = 0.025$). Brain natriuretic peptide levels were significantly higher in the HF-REF patient group ($P = 0.001$). More patients with HF-REF were classified as NYHA functional Class III–IV at discharge than patients with HF-PEF ($P < 0.001$) (*Table 1*).

Table 1 Demographic and clinical characteristics of the matched patient groups at discharge

	HF-REF ($n = 145$)	HF-PEF ($n = 145$)	*P*-value
Demographics			
Age (years)	72 ± 10	72 ± 10	0.739
Female	41%	41%	1.000
Clinical characteristics			
LVEF%	26 ± 7	50 ± 8	<0.001
NYHA III–IV	61%	38%	<0.001
BNP (pg/mL) median (IQR)	516 (290–1125)	370 (215–755)	0.001
Hypertension	37%	50%	0.025
Ischaemic heart failure	43%	43%	0.946
Myocardial infarction	46%	37%	0.095
Duration of heart failure (years)	2.7 ± 4.3	2.7 ± 4.5	0.853
Medication			
ACE-inhibitors/ARB	88%	81%	0.102
Beta-blockers	67%	66%	0.901
Diuretics	97%	97%	1.000
Comorbidities			
COPD	22%	30%	0.109
Diabetes	30%	28%	0.699
Stroke	10%	7%	0.394

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; IQR, inter-quartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease

Quality of life

Global well-being, as measured with Cantril's Ladder of Life, did not differ significantly between patients with HF-PEF and HF-REF (6.3 vs. 6.3, $P = 0.862$).

Scores of all dimensions of the RAND-36 varied between 17 and 78, on the theoretical range between 0 and 100, with the lowest scores for role limitations physical, physical functioning, and health change. None of the dimensions of the general QoL, measured with RAND-36, differ significantly between HP-REF and HF-REF patients, except for bodily pain (HF-PEF vs. HF-REF, 70 vs. 78, $P = 0.006$).

The mean score on the total scale of the MLwHF was 41. On the physical and emotional subscales, mean scores were 21 and 8, respectively. Also on the MLwHF questionnaire, patients with HF-PEF did not rate their QoL different than patients with HF-REF. The total scores as well as the scores on the physical and emotional functioning subscales did not differ significantly between both groups (*Table 2*).

Relationship between brain natriuretic peptide and quality of life

Global well-being was not significantly related to BNP levels in the total patient group ($n = 290$). Of the dimensions of the RAND-36, health change was significantly correlated to BNP levels ($\rho = 0.124$, $P < 0.05$). All other dimensions of the RAND-36 were not significantly correlated to BNP levels. Disease-specific QoL, as measured by means of the MLwHF questionnaire, was significantly correlated with BNP levels. There was a correlation with the total score ($\rho = 0.132$, $P < 0.05$) and the physical subscale of the MLwHF questionnaire ($\rho = 0.151$, $P < 0.01$). There was no significant correlation between BNP levels and the emotional subscale of the MLwHF questionnaire.

Adjustment for brain natriuretic peptide

After adjusting the QoL scores for BNP level, QoL was not associated with LVEF. There were no differences in the adjusted global well-being scores between patients with HF-PEF and HF-REF (6.3 vs. 6.3, $P = 0.671$) (*Figure 1*). The adjusted general QoL did not differ between the two groups, except for the bodily pain dimension, in which patients with HF-PEF had a significantly lower score, which means worse QoL (70 vs. 77, $P = 0.020$) (*Figure 1*) compared with the HF-REF. The scores on the disease-specific QoL questionnaire (MLwHF) did not differ on the total score or on both subscales (physical and emotional functioning) between the two groups (*Figure 1*).

Discussion

The main finding of the present study is that QoL in patients with HF-PEF is as severely affected as it is in patients with HF-REF. This

Table 2 Quality of life in heart failure patients with reduced ejection fraction and heart failure patients with preserved ejection fraction

	Total (n = 290)		HF-REF (n = 145)		HF-PEF (n = 145)		*P*-value[a]
	Baseline	1 month	Baseline	1 month	Baseline	1 month	
Ladder of Life							
Well-being	6.3 ± 2	6.3 ± 2	6.5 ± 2	6.3 ± 2	6.2 ± 2	6.3 ± 1	0.866
RAND-36							
Physical functioning	34 ± 27	40 ± 28	32 ± 27	38 ± 27	35 ± 27	43 ± 28	0.165
Social functioning	53 ± 32	57 ± 29	51 ± 33	55 ± 31	55 ± 31	59 ± 27	0.296
Role limitations physical	18 ± 33	20 ± 34	19 ± 33	17 ± 33	17 ± 33	22 ± 35	0.156
Role limitations emotional	51 ± 45	48 ± 46	53 ± 46	48 ± 46	50 ± 46	49 ± 46	0.807
Mental health	67 ± 23	70 ± 21	67 ± 24	69 ± 21	66 ± 21	70 ± 20	0.908
Vitality	41 ± 23	49 ± 23	42 ± 25	48 ± 23	39 ± 22	49 ± 23	0.938
Bodily pain	63 ± 33	74 ± 28	66 ± 32	78 ± 26	61 ± 33	70 ± 28	0.006
General health	44 ± 18	45 ± 19	44 ± 17	45 ± 19	44 ± 19	45 ± 19	0.956
Health change	26 ± 23	34 ± 29	25 ± 23	34 ± 29	27 ± 23	34 ± 29	0.817
Minnesota Living with Heart Failure							
Total	45 ± 21	41 ± 22	46 ± 21	41 ± 23	44 ± 21	41 ± 21	0.816
Physical functioning	24 ± 10	21 ± 11	25 ± 10	21 ± 11	24 ± 11	20 ± 11	0.704
Emotional functioning	7 ± 6	8 ± 6	7 ± 6	8 ± 6	7 ± 6	8 ± 6	0.692

[a]Comparison between HF-REF and HF-PEF patient groups at 1 month after discharge.

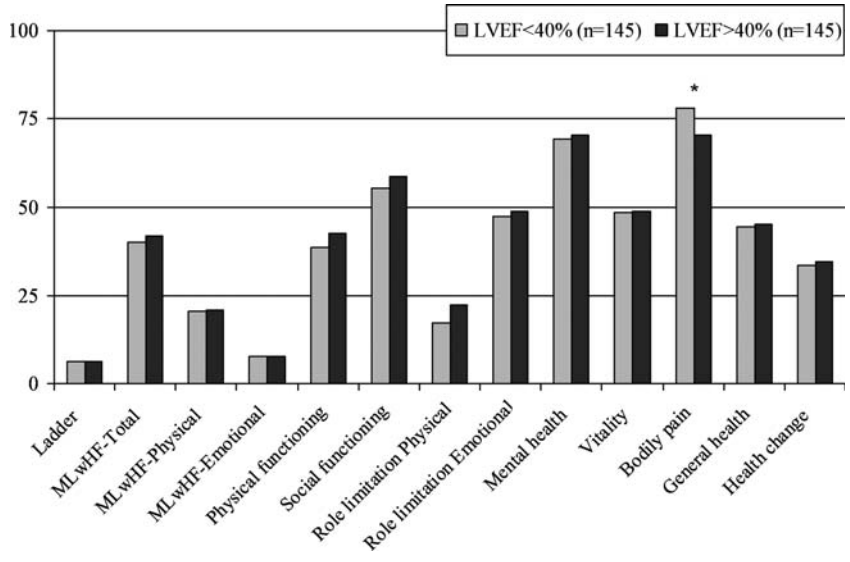

Figure 1 Quality of life in patients with HF-REF (LVEF <40%) and HF-PEF (LVEF ≥40%), multivariate tested and adjusted for brain natriuretic peptide. *$P < 0.05$. HF-REF, heart failure patients with reduced ejection fraction; HF-PEF, heart failure patients with preserved ejection fraction HF

similarity between HF-PEF and HF-REF patients is consistent on several domains of QoL, both disease generic and disease specific. When we adjusted the QoL scores for BNP, as a marker for the severity of the disease, an association between QoL and LVEF was not found, despite the significant correlation between BNP and several QoL domains (health change of the RAND-36, physical and total scores of the MLwHF questionnaire), i.e. patients with HF-PEF and HF-REF with similar BNP levels, had the same impairment in QoL.

Although the two patient groups differed significantly in terms of the number of patients in NYHA III–IV at discharge, and a linear association between NYHA and (physical) QoL could be

suggested, we did not find significant differences in QoL scores. This might be due to the fact that QoL includes more dimensions than physical function alone as measured by NYHA functional class. Although NYHA functional class definitely influences QoL, e.g. the scores between both groups differed the most for the physical function dimensions, the QoL scores between the two groups did not differ significantly.

It is well known that QoL is affected by gender and age and patients with HF-PEF and HF-REF are different regarding these two variables. Patients with HF-PEF are more often female and older[9,10] and in general it would seem that QoL is lower in patients with HF-PEF. By using the matching technique (on age and gender[23]) we showed, however, that possible differences in QoL are not due to differences in LVEF but probably caused by the presence of more patients with higher age and female sex in the HF-PEF group compared with the HF-REF group.

To our knowledge this is the first study to compare QoL between HF-PEF and HF-REF patients, which has used an independent and reliable marker for the severity of HF (i.e. BNP). Although the diagnosis of HF in the COACH study was already well defined, in the current study we only included patients with plasma BNP levels >100 pg/mL. In previous studies, HF patients were defined using more subjective criteria such as NYHA class or an admission to the hospital with a cardiovascular problem in the previous 6 months,[13] an admission to the cardiology ward with symptoms of HF,[11] the application of the European Study Group criteria[12], or a clinical score of three or greater from NHANES I (National Health and Nutrition Examination Survey I).[14,15] There are several possible subjective and objective markers of disease severity in HF, for example, NYHA functional class, sodium restriction, and renal dysfunction. We chose to use BNP levels as a marker of disease severity in our analysis, because this is an objective and a generally accepted measure for the severity of HF,[1] and has no direct overlap with (physical dimensions of) QoL like NYHA functional class.

There are almost no studies published on the comparison of QoL between HF-PEF and HF-REF. One of the few studies that have been published is by Lewis *et al.*[13] from the large CHARM population ($n = 2709$), who reported that QoL was associated with LVEF and was equally impaired in HF-PEF and HF-REF. Our results further extend the findings of this previous study in several aspects. First, our study had the advantage of using an objective marker for the presence of HF (LVEF combined with elevated BNP levels in both the HF-PEF and HF-REF groups), making us more confident that the patients with HF-PEF had HF and were not suffering from different diagnoses. Secondly, our study extends previous observations by using multiple QoL assessments to demonstrate the similarity in different domains of QoL, such as general well-being, physical and social functioning, role limitations, and disease-specific QoL between the two groups. Thirdly, we deliberately chose to match the two patient groups instead of putting age and gender into the multivariate model to have a fair test of comparison. In QoL research between groups of patients, statistical analyses often ignore the meaning of differences in age and gender. When age and gender are treated as nuisance variables and are dealt with by statistical control, we are actually forming a counterfactual situation. In this sense 'controlling for age and gender' substantively means attempting to eliminate the effects of significant differences in role responsibilities.[23] Quality of life is experienced differently by men and women, and by younger and older patients, and therefore we decided to match the two patient groups instead of controlling for age.

While patients with HF-PEF appear to have similar symptoms of HF and their prognosis is as poor as those with HF-REF[9,10,24], no treatment option has been proven effective in this population. Although favourable effects on clinical endpoints (hospitalizations and mortality) have been suggested in some (sub-) populations of patients with HF-PEF for angiotensin-converting enzyme inhibitors,[25] angiotensin receptor blockers,[26] and beta-blockers,[27] none of these agents has shown a significant benefit on outcome in large randomized studies, and none of them has therefore received a recommendation in current guidelines.[1] When it comes to QoL, few studies have focused specifically on the HF-PEF population. Nevertheless, it appears that QoL is gaining increasing attention in HF-PEF, and in one recently reported study with valsartan[28] and in another ongoing study with spironolactone,[29] QoL is one of the important endpoints.

There are a few limitations to the present study. First, due to the process of matching 195 patients, mostly patients with HF-REF, were excluded from the analysis. However, we deliberately chose to match the two patient groups instead of including age and gender in the multivariate analysis to have a fair test of comparison, and gain a more representative clinical insight in the comparison of QoL between patients with HF-PEF and HF-REF.[23] Secondly, we defined HF-PEF as an LVEF $\geq$40%. At present, the cut-off point of LVEF to diagnose HF-REF or HF-PEF is still a matter of debate, we chose a cut-off of 40% because it has been used in other large databases,[13] and because otherwise very few patients would have been included in the HF-PEF group. Thirdly, in the current study we used QoL data at 1 month after discharge, while BNP levels were collected at discharge. We deliberately chose to use the QoL data at 1 month after discharge to minimize the confounding effect of the recent hospitalization.

In conclusion, patients with symptomatic HF with preserved LVEF (HF-PEF) and elevated levels of BNP suffer from their HF as much as age- and gender-matched HF patients with HF-REF, resulting in a comparably low QoL and well-being. Pharmacological and non-pharmacological management interventions that have proved to be successful in HF-REF patients to improve QoL might also be successful in HF-PEF too. Further research to test whether these interventions can improve QoL is now needed.

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